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International Bureau of WIPO  
PCT Receiving Office Section  
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Switzerland

date 30 August 2005  
your ref  
our ref 61.81204/01

Dear Sirs

**International (PCT) Patent Application No. PCT/GB2004/002706 (WO05/000862)**  
**Isis Innovation Limited**

The applicants submit the following comments on the Written Opinion of the International Searching Authority. A Demand for International Preliminary Examination is **not** being filed.

None of documents D1-D4 are relevant to the novelty of claims 4, 6, 8-11, and 17-28. Thus, none of these documents disclose any selenenylsulfide compounds or reactions involving selenenylsulfide chemistry. Furthermore, none of these documents disclose use of any carbohydrate derivatives as referred to in present claims 4 and 8.

Document D5 is not relevant to novelty. It discloses the use of alkyl thiosulfonates for forming disulfide bonds, and in particular for use in glycosylating proteins. The use of any alkyl thiosulfonates is excluded from claims 1, 3 and 8 due to the provisos therein. This document does not disclose any selenenylsulfide chemistry.

D6 does disclose one compound (compound 34) which falls within present claims 8-10. However, this compound is only produced as an unwanted side product. There is no disclosure of the use of this compound in a method of forming a disulfide bond, or for chemically modifying a protein, peptide or amino acid. D6 is not therefore relevant to the novelty of any of the other claims of the application.

D7 discloses the use of bromomethyl benzyl selenide and bromomethyl benzyl sulfide as alkylating agents. The applicants do not agree that D7 discloses the reaction of a selenenylsulfide compound with a thiol compound to produce a disulfide compound. It appears that the citation of this document against claims 1, 6 and 15 is incorrect, and that claims 1, 6 and 15 are in fact novel over D7.

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D8 was published between the two priority dates of the present application. It is therefore not prior art against subject matter which can claim the first priority date. D9 was not published until after both priority dates of the present application. The applicants believe that all the claims of the present application can validly claim priority, and that therefore D9 is not prior art.

It is submitted that there is no lack of inventive step for claims 1 and 3 insofar as R denotes a carbohydrate group and X denotes SO<sub>2</sub>. The only glycosylated alkyl thiosulfonates specifically disclosed in D5 are glycosylated methane thiosulfonates (see page 16 of D5). Example 57 in the present application compares glycosylated methane thiosulfonate reagents as disclosed in D5 with glycosylated phenyl thiosulfonate reagents of the present invention. Example 57 demonstrates that the phenyl thiosulfonate reagents of the present invention can be synthesised in superior yields compared to the corresponding methane thiosulfonate reagents. Furthermore, synthesis of the glycosylated phenyl thiosulfonate reagents is significantly cheaper than synthesis of the corresponding glycosylated methane thiosulfonates. In addition, the reactions carried out with the glycosylated phenyl thiosulfonate reagents of the invention proceeded in a higher yield than the corresponding reactions utilising a methane thiosulfonate reagent.

There is nothing in D5 to suggest to a skilled person the surprisingly superior results achieved using the glycosylated phenyl thiosulfonates of the present invention instead of the methane thiosulfonates disclosed in D5. None of D1-D4 is concerned with glycosylation reactions. There is therefore no lack of inventive step for *inter alia* present claim 4 over any of D1-D5.

It is submitted that there is also no lack of inventive step for present claims 1 and 3 insofar as reactions wherein X denotes Se are involved. As previously mentioned, D7 does not disclose any reactions involving selenenylsulfide compounds. D7 is not therefore relevant to inventive step. Furthermore, there is nothing in D1-D5 to suggest to a skilled person that selenenylsulfide reagents could be used in place of the thiosulfonate reagents used therein. There is therefore no lack of inventive step for *inter alia* present claim 6.

It is submitted that D6 is not relevant to the inventive step of present claim 14. As previously mentioned, compound 34 in D6 is an unwanted side product. The desired product of the reaction was the disaccharide compound 31. A skilled person reading D6 would have no incentive to investigate alternative methods for synthesising selenenylsulfide compounds. Therefore, there can be no lack of inventive step for the method of claim 14 in light of D6.

Yours faithfully  
Frank B. Dehn & Co.

Annabel R. Beacham

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